

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/35</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/56373</b> <b>(43) International Publication Date:</b> 17 December 1998 (17.12.98)
<b>(21) International Application Number:</b> PCT/US98/10605 <b>(22) International Filing Date:</b> 26 May 1998 (26.05.98) <b>(30) Priority Data:</b> 08/873,314 11 June 1997 (11.06.97) US <b>(71)(72) Applicant and Inventor:</b> GORBACH, Sherwood, L. [US/US]; 31 Perry Lane, Weston, MA 02193 (US). <b>(74) Agents:</b> CLARK, Paul, T. et al.; Clark & Elbing LLP, 176 Federal Street, Boston, MA 02110 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> ISOFLAVONOIDS FOR TREATMENT AND PREVENTION OF AGING SKIN AND WRINKLES  <b>(57) Abstract</b>  A method of treating or preventing, in a person, one or more symptoms of aging skin, said method comprising topically administering to the skin of said person a composition comprising one or more isoflavonoids selected from the group consisting of genistein, daidzein, biochanin A, formononetin, O-desmethylangolensin, glycitin, and equol, in a topically acceptable base, wherein the isoflavonoid concentration is between 1 and 40 mg per gram of base.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

## ISOFLAVONOIDS FOR TREATMENT AND PREVENTION OF AGING SKIN AND WRINKLES

### 5 BACKGROUND OF THE INVENTION

The present invention relates to therapies for the prevention and treatment of aging skin and wrinkles.

It has long been recognized that as people grow older, significant changes occur in their skin, specifically thinning, deepening of facial creases  
10 (wrinkling), and increased extensibility and flaccidity. These changes are related to reduced skin tonicity and diminished skin hydration. The underlying causes for these changes are believed to be lowered collagen content and reduced number of elastic fibers in the skin. Estrogen hormones have been used for treating aging skin either in an oral form or as topical skin creams or  
15 gels. These treatments have produced augmented skin thickness, greater hydration, and improvements in elasticity and firmness. It is believed that the effectiveness of estrogen hormones is related to the increase in the amount of skin collagen which is caused by stimulating collagen synthesis. Besides being able to demonstrate the increase in collagen content after estrogen treatment,  
20 there is also an increase in collagen and elastic fibers, which improve the mechanical properties of skin. While estrogen can be used for treating and preventing aging skin, potential users of this hormone are concerned about the risk of side effects, particularly the increased risk of cancers of the breast and uterus. In addition, estrogen typically is not used in men, who also have  
25 problems with aging skin and wrinkles, because of the undesirable side effects of this female hormone in male users. Safer and effective therapies for treating and preventing aging skin and wrinkles in both women and men continue to be sought.

-2-

## SUMMARY OF THE INVENTION

The invention features the topical use of purified isoflavonoids, which are constituents of soy beans and other plants such as clover, to effectively treat and prevent symptoms of aging skin, such as wrinkles. Without being bound  
5 by any theory, it is believed that isoflavonoids have significant estrogenic activity, acting in the skin by stimulating the synthesis of collagen. These compounds are safe and cause no significant side-effects. Purified isoflavonoids which may be administered according to the invention include genistein, daidzein, biochanin A, formononetin, O-desmethylangolensin,  
10 glycitin, and equol; these may be administered alone or in combination.

Accordingly, the invention provides a method of treating or preventing, in a person, one or more symptoms of aging skin, e.g., wrinkles, by applying to the person's skin a composition containing a dermatologically acceptable base containing between 1 and 40 mg purified isoflavonoid per gram of base; the  
15 isoflavonoid is one of the naturally-occurring isoflavonoids listed above.

By "purified" is meant the isoflavonoid is in a form which is more concentrated than the form in which it occurs naturally in plants.

Preferred topical formulations are creams, ointments, lotions, emollient creams and ointments, moisturizing lotions, and gels. The purified  
20 isoflavonoids can also be included in a transdermal delivery system or patch.

The purified isoflavonoids of the invention can also be included in cosmetics (e.g., makeup); preferred forms are lotions, creams, moisturizing creams and lotions, skin oils, skin sprays, and gels.

Preferably, the topical composition containing the purified isoflavonoids  
25 is applied to the skin once or twice per day.

Alternatively, the invention features a method for treating or preventing one or more symptoms of aging skin in a male person or a female person three

-3-

or more years past the onset of menopause, by administering (preferably orally) to the person a composition containing one or more purified isoflavonoids selected from the group consisting of genistein, daidzein, biochanin A, formononetin, O-desmethylangolensin, glycitin, and equol, in an amount

5 sufficient to produce a transient concentration of the bloodstream of the person of at least 50 nm/l. Preferably, the composition is administered orally, providing a dosage of at least 20 mg of total isoflavonoid per serving. The orally-administerable composition can be a non-naturally occurring dietary product such as a confectionary bar, cereal, biscuit, or beverage. Alternatively,

10 the composition can take the form of a medicament such as a pill, capsule, tablet, powder, or syrup, in which the total isoflavonoid is present in at least an amount of 20 mg per unit dose. Preferably, the composition provides a dosage of at least 20 mg of total isoflavonoid per serving. The orally-administerable composition can be a non-naturally occurring dietary product such as a

15 confectionary bar, cereal, biscuit, or beverage. Alternatively, the composition can take the form of a medicament such as a pill, capsule, tablet, powder, or syrup, in which the total isoflavonoid is present in at least an amount of 20 mg per unit dose. Preferably, the dietary product or medicament is orally consumed by the person once, twice, or three times per day, to provide a daily

20 oral isoflavonoid dose of between 20 and 300 mg. Preferably, the oral ingestion of the composition is sufficient to produce a transient concentration in the bloodstream of the person of at least 50 nm of total isoflavonoid per liter of blood. By "purified" isoflavonoid is meant an isoflavonoid in more concentrated form than occurs in plants.

25 Other features and advantages of the invention will be apparent from the Detailed Description thereof, and from the claims.

### DETAILED DESCRIPTION

Isoflavonoids are naturally occurring compounds, found primarily in soy beans. These compounds are also found in high concentrations in red clover and in lower amounts in many other types of plants. An isoflavonoid-  
5 containing fraction (containing purified isoflavonoids) useful in the invention can be extracted from a soy or plant product using known methods. It is preferred that the isoflavonoids be extracted and concentrated from soy beans or soy powder, but other plants such as clover can be used. Isoflavonoids are also available commercially in substantially pure form.

10 The purified isoflavonoid, in the dermatologically acceptable base, is applied directly to the skin surface. The topical composition should be left on the skin for a sufficient period of time to allow the isoflavonoid to be substantially absorbed into the skin and the capillaries supplying the skin; generally, this period of time should be at least one, and preferably at least  
15 three hours. Where the topical composition is a cosmetic, it can be removed in the manner of ordinary cosmetics, e.g., using "cold cream." Because the isoflavonoids are not toxic, the topical composition can be applied at bedtime and left on the face, or other skin surface, overnight.

The isoflavonoid-containing composition can also be included in a  
20 transdermal delivery system or patch. The transdermal patch can be of conventional form, e.g., that used to deliver sustained doses of nicotine or estrogen.

Isoflavonoids have similar chemical properties to estrogens, e.g., they are poorly soluble in water but are readily soluble in alcohols and other organic  
25 solvents. For topical applications, either as a medicament or incorporated into a cosmetic, isoflavonoid is mixed in a base with ingredients such as alcohol, mineral oil, glyceryl monostearate, ether complex of fatty acids, cetyl alcohol,

-5-

lanolin, propylene glycol, stearyl alcohol, and sodium lauryl sulfate. The concentration of isoflavonoid is 1 to 40 mg per gram of the base, more preferably 10-25 mg per gram of base.

Other embodiments are within the claims.

-6-

We claim:

1. A cosmetic composition for application to the surface of the skin of a person for prevention or treatment of symptoms of aging skin, said cosmetic composition comprising a dermatologically acceptable base containing between  
5 1 and 40 mg per gram of base of one or more purified isoflavoids selected from the group consisting of genistein, daidzein, biochanin A, formononetin, O-desmethylangolensin, glycitin, and equol.
2. The composition of claim 1, wherein said composition is in the form of a cream ointment, lotion, emollient cream or ointment, moisturizing lotion,  
10 or gel.
3. The composition of claim 1, wherein said composition is a cosmetic.
4. The composition of claim 3, wherein said cosmetic is a lotion, cream, moisturizing cream or lotion, oil, skin spray, or gel.
5. The composition of claim 1, wherein said composition is carried on a  
15 transdermal delivery system or patch.
6. Use of one or more purified isoflavonoids selected from the group consisting of genistein, daidzein, biochanin A, formononetin, O-desmethylangolensin, glycitin, and equol in the preparation of a medicament for treating or preventing one or more symptoms of aging skin in a male human  
20 or a female human who is three or more years past the onset of menopause.
7. The use of claim 6, wherein said composition is formulated to be

-7-

administered orally, in a dosage of at least 20 mg of isoflavonoid per serving.

8. The use of claim 6, wherein said composition is in the form of a non-naturally occurring dietary product.

9. The use of claim 8, wherein said produce contains at least 20  
5 mg/serving of said isoflavonoid.

10. The use of claim 8, wherein said dietary product is a confectionary bar.

11. The use of claim 8, wherein said dietary product is a cereal.

12. The use of claim 8, wherein said dietary product is a biscuit.

10 13. The use of claim 8, wherein said dietary product is a beverage.

14. The use of claim 6, wherein said composition is in the form of a medicament.

15. The use of claim 14, wherein said composition contains at least 20 mg/unit dose of isoflavonoid.

15 16. The use of claim 14, wherein said medicament is in the form of a pill, capsule, tablet, powder, or syrup.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/10605

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :A61K 31/35

US CL : 514/456

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/456

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	US 5,603,936 A (MONTE) 18 February, 1997, column 1, lines 5-16; examples 26-37.	1-16
Y	US 4,218,489 A (ZILLIKEN) 19 August, 1980, column 2, lines 32-35; column 5, lines 19-37; column 6, lines 34-45.	1-16
Y	US 5,539,129 A (ZYSAMAN et al.) 23 July, 1996, column 7, lines 30-66; column 8, lines 1-65	1-16
Y,P	US 5,654,011 A (JACKSON et al.) 05 August, 1997, column 4, lines 51-67; column 5, lines 1-14; column 7, lines 50-67; column 8, lines 1-17.	7-16

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*B* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

20 JULY 1998

Date of mailing of the international search report

03 SEP 1998

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

LAKSHMI S. CHANNAVAJALA

Telephone No. (703) 308-1235